Anaemia and CAPD

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- Anemia remains one of the most characteristic and visible manifestations of chronic kidney disease (CKD).
- Renal anemia is generally normocytic and normochromic with bone marrow of normal cellularity.
- The recommended threshold for diagnosing renal anemia is at Hemoglobin (Hb) concentrations of less than 13.5 g/dL in men and less than 12.0 g/dL in women.
- Anemia of renal failure begins early in the development of kidney disease and in some patients is clinically evident by stage 3.

Primary Causes

- **Anaemia associated with ESRD is primarily a failure of kidney endocrine function, resulting in deficient levels of renal Erythropoietin (EPO) production.**
- **Although end-stage kidney continues to produce relatively low levels of EPO, it is incapable of augmenting EPO production adequately in response to an appropriate anaemic hypoxic stimulus.**

Secondary Causes

- Although inadequate production of EPO is of paramount importance in the pathogenesis of anaemia in ESRD, other factors contribute.
- Chief among these are shortened erythrocyte survival, blood loss, iron and other nutritional deficiencies and perhaps the effects of uraemic inhibitors on the stimulatory action of EPO on the bone marrow.
- Gross mechanical factors related of haemodialysis include malocclussion of the roller pump, shearing effects from negative pressures in needles and sublethal thermal injury.

- Acute hemolysis is avoided by using a water supply devoid of chloramine, cooper, zinc, nitrates, and reprocessed dialyzers that are free of residual formaldehyde.
- Premature removal of erythrocytes by the retriculoendothelial system may occur. Rarely, profound splenic sequestration requiring splenectomy occurs.
- Additional contributing factors unique to anaemia in ESRD include those related to nutrition, vitamin deficiencies and the dialysis process.

Tertiary Causes

- **Secondary hyperparathyroidism can lead to myelofibrosis in ESRD patients and affected patients often require high doses of rHuEPO to achieve target hemoglobin levels.**
- **Correction of hyperparathyroidism by parathytoidectomy has been shown to reduce rHuEPO requirements needed to reach adequate hematopoietic response in some ESRD patients.**

- The presence of excess aluminum in the blood may interfere with rHuEPO responsiveness.
- Several studies have shown that the response to rHuEPO is impaired not only in states of frank aluminum overload but at levels previously considered acceptable.

- Nonrenal nondialysis factors: These include malignancy (myeloma, metastatic cancer), haemolysis (sickle cell disease, SLE), infections, inflammation and hypothyroidism. Drug-induced anemias and drug-induced bleeding (NSAIDs).
- Decreased serum levocarnitine levels are associated with rHuEPO hyporesponsiveness.

NKF-K/DOQI Clinical Practice Guidelines and Recommendations for treatment of anemia in ESA-Treated Hemodialysis patients

- Hemoglobin should be 11 g/dL or greater, with insufficient evidence to recommend routinely maintaining hemoglobin levels of 13 g/dL or greater.
- Hemoglobin levels should be monitored at least monthly.
- More frequent monitoring is appropriate for unstable and out-of-target hemoglobin levels, and in hemodialysis patients.
- More initial ESA dose and subsequent ESA dose adjustments should be determined by the patient's hemoglobin level, the target hemoglobinevel, and the rate of increase in hemoglobin level. ESA doses should be decreased, but not necessarily withheld, when a downward adjustment of hemoglobin level in needed. Scheduled ESA doses that have been missed should be replaced at the earliest possible convenience.
- The goal of therapy should be to increase the hemoglobin level by about 1 to 2 g/dL per month.
- Hypertension, vascular access occlusion, inadequate dialysis, history of seizure or compromised nutritional status are not contraindications to ESA therapy.
- Convenience favors intravenous ESA administration in hemodialysis patients.

Adapted from National Kidney Foundation, NKF-K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2007, in press

Treatment of Anemia in Peritoneal Dialysis Patients

- **Effective treatment of anemia in adult and pediatric peritoneal dialysis (PD) patients consists of an erythopoiesis-stimulating agent (ESA) usually in combination with iron supplementation.**
- **However, anemia remains more prevalent in Pediatric compared to adult PD patients.**

Goal of Therapy

- According to The National Kidney Foundation- Kidney Disease Outcomes Quality Intitative (NKF-K/DOQI) clinical practice guidlined, the recommended target hemoglobin value for all dialysis patients is 11.0 g/dL or greater.
- However, safety concerns from recent clinical trials have prompted many clinicians to generally use a target hemoglobin value of 11-12 g/dL.
- Further indicates that to achieve the target hemoglobin value in patients receiving PD a transferrin saturation >20% and a serum ferritin concentration >100 ng/dL should be maintained.

- **In pediatric PD patients recommendations for hemoglobin, transferrin saturation and serum ferritin mimic those for adult patients receiving PD.**
- **Hemoglobin values less than the NKF-K/DOQI-recommended target are associated with increased adjusted mortality hazard ratios and increased risk of adjusted first-hospitalization rate in adult PD patients.**

Dosing and Route of administration of Epoetin

- The intravenous (IV) route of epoetin administration is impractical and infrequently used.
- Subcustaneous administration provides the easiest and most economical route for PD patients.
- Subcutaneous injection into the thigh area may provide the most favorable serum concentration profile, followed by the upper arm (mild-deltoid region) and the abdomen.
- IP dosing is seldom prescribed.
- However, this route of administration remains a suitable option-especially for pediatric PD patients for whom subcutaneous (SC) dosing is distressing.

Dosing and Route of administration of Epoetin

- Epoetin guidelines for PD patients are similar to those of HD patients.
- Generally, an SC starting dose of 30 to 50 U/Kg twice weekly leads to adequate response.
- Does adjustments may be made, usually once a month, by increasing or decreasing the dose of epoetin- or conversely by shortening or lengthening the dosing interval.

Adverse Effects of Epoetin

- Hypertension, the most common adverse event associated with the use of epoetin occurs approximately ¼ of patients.
- A relatively small number of patients who have received epoetin and darbepoetin have developed pure red cell aplasia (PRCA) due to the formation of antierythropoietin-neutralizing antibodies.
- PRCA leads to severe anemia with impaired reticulocyte formation.

- **The development of PRCA has occurred predominantly in patients receiving epoetin or darbepoetin by the SC route.**
- **PRCA should be considered part of the evaluation of sudden loss of response to these erythropoietic hormones.**

Parenteral Iron Administration to PD patients

- Because PD patients do not have ready access for the administration of IV iron, oral iron supplements are commonly prescribed.
- For various reasons, however, many PD patients are unable to remain iron repleced with oral iron therapy alone.

IV Iron Dosing Protocols for Adult PD Patients

	Iron Dextran	Sodium Ferric Gluconate Complex	Iron Sucrose
Test dose recommended	Yes	No	No
Dosing scheme:	25 mg dilutes in 50 mL normal saline: infuse over 30 min. Follow with 475 mg dilutes in 300 mL normal saline; infuse over 4-5 h	125 mg dilutes in 100 mL normal saline; infuse over 60 min 250 mg dilutes in 100 mL saline; infuse over 1 h.	500 mg dilutes in 300 mL normal saline; infuse over 4-6 h 200 mg dilutes in 150 mL normal saline; infuse over 1 h 50 mg undilutes over 5 min
	25 mg dilutes in 50 mL normal saline; infusion over 30 min. Follow with 975 mg diluted in 500 mL ½ normal saline; infuse over 5 h. [b]		200 mg undilutes over 2 min 1000 mg total cummulative dose. Give 2 infusions of 300 mg over 1.5 h 14 d apart followed by one 400 mg infusion over 2.5 h 14 d later. Dilute each dose in a max of 250 mL of normal saline

a. These protocols do not necessaarily conform to FDA-approved product labeling.
b. This dosing scheme may be associated with increased dose-related adverse events.

- **There is very little published information regarding the administration of IV iron to pediatric PD patients. Oral iron is recommended whenever possible.**
- **IP iron dextran administration has been advocated in a few publications. However, due to scarcity of data on long-term safety and efficacy of IP iron in humans this route of administration cannot be recommended at this time.**

Hypertension and Epoetin Use in Dialysis Patients

- Cardiovascular complications remain the leading cause of morbidity and morality in patients with end- stage renal disease (ESRD).
- By raising the left ventricular (LV) afterload, chronic hypertension promotes LV hypertrophy (LVH) and ultimately LV dilation and congestive heart failure.
- In addition, hypertension contributes to coronary arteriosclerosis and ischemic heart disease.

- **Likewise, by necessitating a high cardiac output and hence cardiac workload long-standing severe anemia promotes LVH, which is a major risk factor for cardiovascular complications.**
- **Hypertension and anemia (the two most common features of ESRD) work in concert to impair cardiac function and structure compounding the effects of numerous other risk factors (such as dyslipidemia, hypervolemia oxidative stress, inflammation, hyperhomocystinemia, glucose intolerance, and vascular calcification) frequently present in this population.**

- **Although amelioration of anemia improves the associated high-cardiac output state and LV function/structure, it frequently raises arterial blood pressure.**
- **In addition, r-HuEPO therapy reduces hemodynamic instability during dialysis which when present can limit fluid removal by ultra filtration. Thus, r-HuEPO therapy can enhance the ability to remove excess fluid and achieve euvolemia.**

Clinical Features

- Initial multicenter clinical trials of r-HuEPO revealed a rise in mean arterial blood pressure exceeding 10 mmHg in approximately 70% of the treated patients within 2 weeks to 6 months after the onset of r- HuEPO therapy.
- The observed rise in blood pressure is generally mild to moderate and readily controlled by intensification of fluid removal by ultrafiltration alone, or together with initiation or adjustment of antihypertensive medications.

- Rarely, however, r-HuEPO therapy can cause severe hypertension leading to encephalopathy and seizures requiring hospitalization and intensive antihypertensive therapy, along with a temporary cessation of r-HuEPO therapy.
- Several conditions have been considered associated with an increased risk for development of hypertension with r-HuEPO therapy, including severe pretreatment anemia, preexisting hypertension, high r-HuEPO dosages, use of intravenous as opposed to subcutaneous route of r-HuEPO administration, and possible angiotensinogen gene polymorphisms.

Mechanisms

- Expansion of erythrocyte mass can raise blood volume and thus blood pressure.
- Increased systemic vascular resistance attributed to an increase in blood viscosity from subnormal to near normal levels.
- In addition, loss of hypoxia (anemia) induced vasodilatation.
- Gradual correction of anemia with multiple small red blood cell transfusions designed to simulate the effect of r-HuEPO therapy did not alter blood pressure.

- **It is now clear that r-HuEPO therapy raises both resting and stimulated levels of cytoplasmic ionized calcium $[Ca^{++}]_{i}$, which is the ultimate determinant of vascular smooth muscle tone/reactivity and therapy systemic vascular resistance and blood pressure.**
- **r-HuePO receptors, which are now known to be expressed in erythroid progenitor cells as well as in a wide array of other cell types, including megacaryocytes, vascular smooth muscle cells, and endothelial cells.**

- **Moreover, r-HuEPO raises the level of naturally occurring nitric oxide synthase inhibitor asymmetrical dimethylarginine (ADMA) by inhibiting the activity of dimethylarginine dimethylaminohydrolase (which degrades ADMA).**
- **Consequently, r-HuEPO can reduce production of nitric oxide by vascular endothelial cells.**

- **In addition, r-HuEPO therapy augments the tissue (not circulating) renin-angiotensin system, raises endothelin and vasoconstrictive prostaglandins, and lowers vascodilatory prostaglandins.**
- **Furthermore, r-HuEPO stimulates angiogenesis and vascular cell proliferation in vitro.**
- **Chronic r_HuEPO therapy, therefore, may directly and indirectly (by raising blood pressure) promote vascular remodeling-leading to a fixed in vascular resistance.**

Etiologies of rHuEPO Refractoriness

Occurring Any Time During rHuEPO Therapy	Occurring commonly in the setting of successful chronic rHuEPO Therapy
	- Iron deficiency - Inflammatory blockade. - Aluminum intoxication . - hemoglobin “cycling” - Hyperparathyroidisim - Hemoglobinopathy - Myelophthisic states - Hemolysis - ACEI treatment - Carcitine deficiency - Pure red-cell aplasia - Hemolysis

Adult/Pediatric PD/HD Patient Epoetin Use Patterns from December 2005 ESRD Clinical Performance Measures Project Annual Report

Patient Group	Route of administration (% Patients Prescribed Epoetin)[a]	Mean ± SD Weekly Dose *Units/kg)
Adult PD patients	Subcutaneous: 98 Intravenous: 7	154 ± 150 188 ± 173
Adult HD patients	Subcutaneous: 5 Intravenous: 96	215 ± 233 281 ± 281
Pediatric PD patients	Subcutaneous: 97 Intravenous: 6	228 ± 214 317 ± 218
Pediatric HD patients	Subcutaneous: 10 Intravenous: 91	275 ± 241 364 ± 358

a. Groups not mutually exclusive

Thank You

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